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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 11/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/912,559	ROEMISCH ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky	1652	

-- Th MAILING DATE of this communication appears on the cover sheet with th correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *3-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 30-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9/10/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed September 10, 2003 amending the abstract to correct clerical errors, amending claim 1 and adding claims 30-36 has been entered.

Claims 1-36 are pending. Claims 3-29 are withdrawn. Claims 1, 2 and 30-36 are under examination.

Specification

The abstract of the disclosure is objected to because the word "REPLACEMENT" in the heading "REPLACEMENT ABSTRACT" should be crossed out.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1, with depended claims 30-32 and 34-36, is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is drawn to "a mutant of the nucleotide sequence coding for the factor VII-activating protease (FSAP), comprising at least one of [mutations]". Since "comprising" is open language, claim 1 reads on a mutant comprising any number of mutations in addition to the two specific mutations (1177 and/or 1601) in the wild type sequence of SEQ ID NO:1.This amounts to any nucleotide structure that is not necessarily homologous to SEQ ID NO:1. SEQ ID NO:1 encodes SEQ ID NO:3. Thus, the claim is drawn to an enormous genus of FSAP mutants.

Applicants disclose a single species of said genus of mutants, SEQ ID NO:2, that differs from the wild type SEQ ID NO:1 by a G to C base exchange at nucleotide position 1177 and a G to A base exchange at nucleotide position 1601 resulting in mutations **E393Q** and **G534E** in SEQ ID NO:3, respectively. These mutations correspond to mutations **E370Q** and **G511E**, respectively, in the mature FSAP and are named *Marburg II* and *Marburg I* mutations, respectively (Roemish et al. (2002) Blood Coagulation and Fibrinolysis, 13(50, 433-441, form PTO-1449 filed September 10, 2003, reference 10). The specification teaches various protease activities of FSAP (page 9 and pages 11-12). The specification teaches that G534E mutation in FSAP impairs its *in vitro* ability to activate prourokinase (page 2, penultimate paragraph; pages 4-5, Table 1, especially page 5, penultimate sentence). However, the specification discloses that "whether an amino acid exchange at position 393 only can lead to a reduction in prourokinase activity, is still uncertain at the moment (page 5, last

sentence, emphasis added). Further research showed that "the Marburg I polymorphism, per se, lacks in vitro effects on" prourokinase activity (referenced in Willeit et al. (2003) on page 670, 1st column, form PTO-1449 filed September 10, 2003, reference 8). Therefore, the mutants of FSAP may retain some FSAP activities and lack others. However, the specification fails to describe any other identifying characteristics or properties of mutant FSAPs other than the "functionality" of encoding "a polypeptide with FSAP activity", i.e. any FSAP activity, and fails to provide any structure: function correlation present in all members of the claimed genus.
Claim 31 is construed as drawn to a polynucleotide that differs from SEQ ID NO:1 by at least one mutation selected from the group consisting of G to C base exchange at nucleotide position 1177 and a G to A base exchange at nucleotide position 1601. However, a mutant that differs from SEQ ID NO:1 by a single mutation consisting of G to C base exchange at nucleotide position 1177 is not described in the specification. It describes the single G534E mutant and the double E393Q/G534E mutant (pages 5-6).

Therefore, the specification is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Claim 1 and claims 30-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the nucleotide sequence that differs from SEQ ID NO:1 by G to A base exchange at nucleotide position 1601 and for SEQ ID NO:2 that differs from SEQ ID NO:1 by two mutations at positions 1177 and 1601, does not reasonably provide enablement for a mutant of the nucleotide sequence coding for FSAP, comprising at least one of the two mutations at positions 1177 and 1601 and having unknown homology to SEQ ID NO:1 and encoding a polypeptide with an undefined FSAP activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, how to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7)considered in determining whether undue experimentation is required, are summarized the predictability or unpredictability of the art, and (8) the breadth of the claims.

The specification teaches various protease activities of FSAP (page 9 and pages 11-12).

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of FSAP mutants having unknown structures and undefined activities broadly encompassed by the claims. Since the amino acid/nucleotide sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification teaches that G534E mutation in FSAP impairs its *in vitro* ability to activate prourokinase while E393Q apparently does not (page 2, penultimate

paragraph; pages 4-5, Table 1, especially page 5, two last sentences). Therefore, the mutants of FSAP may retain some FSAP activities and lack others. However, in this case the disclosure is limited to the amino acid sequence of a single mutant having the nucleotide sequence of SEQ ID NO:2. A polypeptide of SEQ ID NO:4 that is encoded by SEQ ID NO:2 apparently lacks prourokinase activating activity (page 5). Therefore, claims 1, 30-32 and 34-36, drawn to the mutants comprising an A at nucleotide position 1601 are not enabled for a polypeptide with a prourokinase activating FSAP activity.

The specification does not support the broad scope of the claims which encompass polynucleotides with unknown homology to SEQ ID NO:1 encoding mutant FSAPs having any FSAP activity because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting a requisite FSAP activity; (B) the general tolerance of FSAP to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any FSAP residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and/or the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of modifications in SEQ ID NO:1.

Without such guidance, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Claim 31 is included in this rejection because of its indefiniteness discussed below.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2 and 30-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2 and 30-36 recite "a polypeptide with FSAP activity". As discussed above, FSAP have various activities, including various protease activities. Without defining the FSAP activity, the metes and bounds of the claims are unclear. For example, claims 30 and 35 are drawn to polynucleotides encoding mutant FSAP that is shown to lack a prourokinase activating activity but possibly having other FSAP activities.

Claim 1 recites "wherein nucleotide positions 1177 and 1601 are defined with reference to SEQ ID NO:1". It is unclear whether sequences other than SEQ ID NO:1

are encompassed by the claim. Amending the claim to recite "nucleotide positions 1177 and 1601 in SEQ ID NO:1" is suggested.

Claims 31 and 32 are unclear because of the following. Claim 31 is construed as drawn to a polynucleotide that differs from SEQ ID NO:1 by at least one mutation selected from the group consisting of G to C base exchange at nucleotide position 1177 and a G to A base exchange at nucleotide position 1601. However, claim 32 that depends from claim 31, recites "the polynucleotide [that] comprises an A at nucleotide 1601" (emphasis added). Such language would allow more than one or two mutations in SEQ ID NO:1.

Claim 34 is redundant as dependent from claim 1 because it has a broader scope. It is appropriate for claim 1 to depend from claim 34.

The term "reduced" in claim 36 is a relative term which renders the claim indefinite. The term "reduced" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear which of various FSAP activities is reduced and to what degree.

Allowable Subject Matter

Claims 2 and 33 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action or rewritten in independent form.

Response to Arguments

Applicant's arguments filed September 10, 2003 have been fully considered but they are not persuasive.

With regard to the written description, Applicants argue that amending the claims to recite "a polypeptide with FSAP activity" "provided appropriate structure/function correlation to characterize this genus" (Remarks, page 11). This is not persuasive for the reasons discussed in details above. FSAP has various activities and the specification provides no structure/function correlation common to all members of the genus. Applicants argue that FSAP activity was screened by examining the ability of the FSAP mutant species to activate prourokinase. Some of the isolates showed reduced FSAP activity, corresponding to new claim 36, for example (Specification at Tables 1 and 2)" (page 11). This is not persuasive because claims are not limited to a prourokinase activating FSAP activity. Furthermore, the only mutant where prourokinase activating FSAP activity is reduced is the G534E mutant (Marburg I mutant). Because the analysis was made using not an isolated G534E mutant

polypeptide but blood from heterozygosities containing the mixture of the mutant an wild type FSAP (specification pages 4-5). It is apparent that an isolated G534E mutant polypeptide or blood from homozygosities would lack prourokinase activating FSAP activity.

With regard to the enablement rejection, Applicants argue that "this prourokinase assay is known in the art" (page 12). It appears that these arguments are misplaced. It is agreed that the prourokinase assay is known in the art but the claims are not drawn to mutant FSAP polypeptides with prourokinase activating activity. Furthermore, as discussed above, the invention is drawn to the mutant lacking said activity. Applicants further argue that mutants are crossreactive with the deposited monoclonal antibodies (page 13). This is not persuasive because first, the claims do not contain the requisite limitation and second, said antibodies do not distinguish between the wild type and/or mutants with various FSAP activities.

With regard to the 112, 2nd paragraph, rejection, Applicants argue that "solely to speed the prosecution, Applicants have amended claim 1, rendering this rejection moot" (page 15). The reasons for rejecting the amended claim 1 are explained in the rejection above.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner